(FILE 'HOME' ENTERED AT 07:48:54 ON 20 FEB 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, AGRICOLA' ENTERED AT 07:49:08 ON 20 FEB 2003

L1	569663	S PROLIFERATION OR VIABILITY
L2	111	S L1 AND IMPDH
L3	81	S L2 AND HUMAN
L4	44	DUP REM L3 (37 DUPLICATES REMOVED)
L5	4	S L4 AND RESISTANT
L6	4	DUP REM L5 (0 DUPLICATES REMOVED)
L7	1	S L2 AND MUTANT
L8	727	S IMPDH
L9	1373	S IMPDH OR (INOSINE (1N) MONOPHOSPHATE (1N) DEHYDROGENASE)
L10	145	S L9 AND MUTA?
L11	79	S L10 AND INHIBIT?
L12	8	S L11 AND (PROLIFERATION OR VIABILITY OR DEATH)
L13	6	DUP REM L12 (2 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 08:03:42 ON 20 FEB 2003

FILE 'MEDLINE, CAPLUS, BIOSIS, AGRICOLA' ENTERED AT 08:05:52 ON 20 FEB 2003

L14 45 DUP REM L11 (34 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 08:10:02 ON 20 FEB 2003

	Type	Hits	Search Text	DBs
1	BRS	7	"1178797"	USPAT; US-PGPUB; EPO; JPO; DERWENT;
2	BRS	33	"0056331"	USPAT; US-PGPUB; EPO; JPO; DERWENT;
3	BRS	7	stamos AND trudeau	USPAT; US-PGPUB; EPO; JPO; DERWENT;
4	BRS	211	impdh	USPAT; US-PGPUB; EPO; JPO; DERWENT;
5	BRS	138	impdh and (proliferation or viability)	USPAT; US-PGPUB; EPO; JPO; DERWENT;
6	BRS	641431	(impdh and (proliferation or viability)) resistant	USPAT; US-PGPUB; EPO; JPO; DERWENT;
7	BRS	93	(impdh and (proliferation or viability)) and resistant	USPAT; US-PGPUB; EPO; JPO; DERWENT;
8	BRS	92	((impdh and (proliferation or viability)) and resistant) and (greater or increase)	USPAT; US-PGPUB; EPO; JPO; DERWENT;
9	BRS	1	"6514979"	USPAT; US-PGPUB; EPO; JPO; DERWENT;
10	BRS	211	impdh	USPAT; US-PGPUB; EPO; JPO; DERWENT;
11	BRS	131	impdh and (mutant or mutation or mutagenized)	USPAT; US-PGPUB; EPO; JPO; DERWENT;
12	BRS	129	(impdh and (mutant or mutation or mutagenized)) and (inhibiting or inhibitor or inhibited)	USPAT; US-PGPUB; EPO; JPO; DERWENT;
13	BRS	102	((impdh and (mutant or mutation or mutagenized)) and (inhibiting or inhibitor or inhibited)) and mammalian	USPAT; US-PGPUB; EPO; JPO; DERWENT;
14	BRS	102	(((impdh and (mutant or mutation or mutagenized)) and (inhibiting or inhibitor or inhibited)) and mammalian) and (proliferation or viability or cell)	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB
15	BRS	0	((((impdh and (mutant or mutation or mutagenized)) and (inhibiting or inhibitor or inhibited)) and mammalian) and (proliferation or viability or cell)) and inosine and monophophate and	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB

	Type	Hits	Search Text	DBs
16	BRS	95	((((impdh and (mutant or mutation or mutagenized)) and (inhibiting or inhibitor or inhibited)) and mammalian) and (proliferation or viability or cell)) and inosine and monophosphate and	USPAT; US-PGPUB; EPO; JPO; DERWENT; IBM_TDB
17	BRS	64084	proliferation or proliferative	USPAT; US-PGPUB; EPO; JPO; DERWENT;
18	BRS	65370	proliferation or proliferative or antiproliferative	USPAT; US-PGPUB; EPO; JPO; DERWENT;
19	BRS	50590	(proliferation or proliferative or antiproliferative) and cell	USPAT; US-PGPUB; EPO; JPO; DERWENT;
20	BRS	6	5,536,747	USPAT; US-PGPUB; EPO; JPO; DERWENT;
21	BRS	643	"l6" and (antiproliferative or proliferation or proliferative)	USPAT; US-PGPUB; EPO; JPO; DERWENT;
22	BRS	6	5,536,747 and (antiproliferative or proliferation or proliferative)	USPAT; US-PGPUB; EPO; JPO; DERWENT;
23	BRS	137	proliferation and impdh	USPAT; US-PGPUB; EPO; JPO; DERWENT;
24	BRS	19	proliferation near4 impdh	USPAT; US-PGPUB; EPO; JPO; DERWENT;
25	BRS	2478	cell near2 proliferation near2 assay	USPAT; US-PGPUB; EPO; JPO; DERWENT;
26	BRS	23	human near2 cell near2 proliferation near2 assay	USPAT; US-PGPUB; EPO; JPO; DERWENT;

L4 ANSWER 12 OF 44 MEDLINE
AN 2001245009 MEDLINE
DN 21129359 PubMed ID: 11233304
TI Pharmacological profiles of mycophenolate mofetil (CellCept), a new immunosuppressive agent.
AU Yashima Y; Ohgane T
CS Nippon Roche Research Center, Nippon Roche K.K., 200 Kajiwara, Kamakura City, Kanagawa 247-8530, Japan.. yukihiko.yashima@roche.com
SO NIPPON YAKURIGAKU ZASSHI. FOLIA PHARMACOLOGICA JAPONICA, (2001 Feb) 117 (2) 131-7. Ref: 25
Journal code: 0420550. ISSN: 0015-5691.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Japanese
FS Priority Journals
EM 200105
ED Entered STN: 20010517
Last Updated on STN: 20010517
Entered Medline: 20010510
AB Mycophenolate mofetil (MMF, CellCept), a semisynthetic derivative of mycophenolic acid (MPA) produced by a fungus, is an inhibitor of the inosine monophosphate dehydrogenase (**IMPDH**) enzyme (IC50 = 25 nM) that catalyzes the synthesis of guanosine monophosphate (GMP) from inosine. GMP is an essential nucleoside for purine synthesis during cell division. As T and B-lymphocytes almost exclusively use the de novo pathway of purine synthesis, these cells are particularly sensitive to the inhibitory action of MMF. It has a mechanism of action distinct from cyclosporine and tacrolimus. Although MMF does not affect cytokine production, by inhibiting the rate-limiting enzyme **IMPDH** in the de novo synthesis of purines, it inhibits the **proliferation** of T and B-lymphocytes, the production of antibodies, and the generation of cytotoxic T lymphocytes. Reversal of acute allograft rejection and increased survival of kidney, heart and bone marrow cell allograft has been shown in several animal studies. Moreover, it was suggested that MMF combined with CsA prevented the acute rejection, and approximately half of the animals became long-term survivors. The Ministry of Health and Welfare approved MMF in 1999 for use for rejection treatment in renal transplantation based on several prospective, randomized and blind efficacy trials.

L14 ANSWER 35 OF 45 MEDLINE DUPLICATE 13
AN 96279836 MEDLINE
DN 96279836 PubMed ID: 8681386
TI Structure and mechanism of **inosine monophosphate dehydrogenase** in complex with the immunosuppressant mycophenolic acid.
AU Sintchak M D; Fleming M A; Futer O; Raybuck S A; Chambers S P; Caron P R; Murcko M A; Wilson K P
CS Vertex Pharmaceuticals Incorporated, Cambridge, Massachusetts 02139-4211, USA.
SO CELL, (1996 Jun 14) 85 (6) 921-30.
Journal code: 0413066. ISSN: 0092-8674.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U13372
EM 199608
ED Entered STN: 19960828
Last Updated on STN: 19960828
Entered Medline: 19960816
AB The structure of **inosine**-5'-**monophosphate dehydrogenase (IMPDH)** in complex with IMP and mycophenolic acid (MPA) has been determined by X-ray diffraction. **IMPDH** plays a central role in B and T lymphocyte replication. MPA is a potent **IMPDH inhibitor** and the active metabolite of an immunosuppressive drug recently approved for the treatment of allograft rejection. **IMPDH** comprises two domains: a core domain, which is an alpha/beta barrel and contains the active site, and a flanking domain. The complex, in combination with **mutagenesis** and kinetic data, provides a structural basis for understanding the mechanism of **IMPDH** activity and indicates that MPA **inhibits** **IMPDH** by acting as a replacement for the nicotinamide portion of the nicotinamide adenine dinucleotide cofactor and a catalytic water molecule.

L14 ANSWER 35 OF 45 MEDLINE DUPLICATE 13
AN 96279836 MEDLINE
DN 96279836 PubMed ID: 8681386
TI Structure and mechanism of **inosine monophosphate dehydrogenase** in complex with the immunosuppressant mycophenolic acid.
AU Sintchak M D; Fleming M A; Futer O; Raybuck S A; Chambers S P; Caron P R; Murcko M A; Wilson K P
CS Vertex Pharmaceuticals Incorporated, Cambridge, Massachusetts 02139-4211, USA.
SO CELL, (1996 Jun 14) 85 (6) 921-30.
Journal code: 0413066. ISSN: 0092-8674.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U13372
EM 199608
ED Entered STN: 19960828
Last Updated on STN: 19960828
Entered Medline: 19960816
AB The structure of **inosine**-5'-**monophosphate dehydrogenase** (**IMPDH**) in complex with IMP and mycophenolic acid (MPA) has been determined by X-ray diffraction. **IMPDH** plays a central role in B and T lymphocyte replication. MPA is a potent **IMPDH inhibitor** and the active metabolite of an immunosuppressive drug recently approved for the treatment of allograft rejection. **IMPDH** comprises two domains: a core domain, which is an alpha/beta barrel and contains the active site, and a flanking domain. The complex, in combination with **mutagenesis** and kinetic data, provides a structural basis for understanding the mechanism of **IMPDH** activity and indicates that MPA **inhibits** **IMPDH** by acting as a replacement for the nicotinamide portion of the nicotinamide adenine dinucleotide cofactor and a catalytic water molecule.

L14 ANSWER 34 OF 45 MEDLINE DUPLICATE 12
AN 97150852 MEDLINE
DN 97150852 PubMed ID: 8995388
TI Isolation and characterization of mycophenolic acid-resistant **mutants** of **inosine**-5'-**monophosphate dehydrogenase**.
AU Farazi T; Leichman J; Harris T; Cahoon M; Hedstrom L
CS Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254, USA.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Jan 10) 272 (2) 961-5.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199702
ED Entered STN: 19970227
Last Updated on STN: 19970227
Entered Medline: 19970212
AB Mycophenolic acid (MPA) is a potent and specific **inhibitor** of mammalian **inosine-monophosphate dehydrogenases** (**IMPDH**); most microbial **IMPDHs** are not sensitive to MPA. MPA-resistant **mutants** of human **IMPDH** type II were isolated in order to identify the structural features that determine the species selectivity of MPA. Three **mutant IMPDHs** were identified with decreased affinity for MPA The **mutation** of Gln277 --> Arg causes a 9-fold increase in the Ki of MPA, a 5-6-fold increase in the Km values for IMP and NAD, and a 3-fold decrease in kcat relative to wild type. The **mutation** of Ala462 --> Thr causes a 3-fold increase in the Ki for MPA, a 2.5-fold increase in the Km for NAD, and a 1.5-fold increase in kcat. The combination of these two **mutations** does not increase the Ki for MPA, but does increase the Km for NAD 3-fold relative to Q277R and restores kcat to wild type levels. Q277R/A462T is the first human **IMPDH mutant** with increased Ki for MPA and wild type activity. The third **mutant IMPDH** contains two **mutations**, Phe465 --> Ser and Asp470 --> Gly. Ki for MPA is increased 3-fold in this **mutant** enzyme, and Km for IMP is also increased 3-fold, while the Km for NAD and kcat are unchanged. Thus increases in the Ki for MPA do not correlate with changes in Km for either IMP or NAD, nor to changes in kcat. All four of these **mutations** are in regions of the **IMPDH** that differ in mammalian and microbial enzymes, and thus can be structural determinants of MPA selectivity.

4 ANSWER 24 OF 45 MEDLINE
AN 2000437520 MEDLINE
DN 20411273 PubMed ID: 10953035
TI **Inhibition** of T lymphocyte activation in mice heterozygous for loss of the **IMPDH** II gene.
AU Gu J J; Stegmann S; Gathy K; Murray R; Laliberte J; Ayscue L; Mitchell B S
CS Lineberger Comprehensive Cancer Center, Department of Pathology, University of North Carolina, Chapel Hill, North Carolina 27599, USA.
NC KO8CA64444 (NCI)
RO1CA64192 (NCI)
SO JOURNAL OF CLINICAL INVESTIGATION, (2000 Aug) 106 (4) 599-606.
Journal code: 7802877. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200009
ED Entered STN: 20000928
Last Updated on STN: 20000928
Entered Medline: 20000918
AB **Inosine** 5'-**monophosphate dehydrogenase** (**IMPDH**) is the rate-limiting enzyme in the de novo synthesis of guanine nucleotides, which are also synthesized from guanine by a salvage reaction catalyzed by the X chromosome-linked enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT). Since **inhibitors** of **IMPDH** are in clinical use as immunosuppressive agents, we have examined the consequences of knocking out the **IMPDH** type II enzyme by gene targeting in a mouse model. Loss of both alleles of the gene encoding this enzyme results in very early embryonic lethality despite the presence of **IMPDH** type I and HPRT activities. Lymphocytes from **IMPDH** II(+/-) heterozygous mice are normal with respect to subpopulation distribution and respond normally to a variety of mitogenic stimuli. However, mice with an **IMPDH** II(+/-), HPRT(-/o) genotype demonstrate significantly decreased lymphocyte responsiveness to stimulation with anti-CD3 and anti-CD28 antibodies and show a 30% mean reduction in GTP levels in lymphocytes activated by these antibodies. Furthermore, the cytolytic activity of their T cells against allogeneic target cells is significantly impaired. These results demonstrate that a moderate decrease in the ability of murine lymphocytes to synthesize guanine nucleotides during stimulation results in significant impairment in T-cell activation and function.

DN 20031537 PubMed ID: 10563825
TI Species-specific **inhibition** of **inosine** 5'-**monophosphate dehydrogenase** by mycophenolic acid.
AU Digits J A; Hedstrom L
CS Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02454, USA.
NC GM07956 (NIGMS)
GM54403 (NIGMS)
SO BIOCHEMISTRY, (1999 Nov 16) 38 (46) 15388-97.
Journal code: 0370623. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991220
AB **IMPDH** catalyzes the oxidation of IMP to XMP with the concomitant reduction of NAD(+) to NADH. This reaction is the rate-limiting step in de novo guanine nucleotide biosynthesis. Mycophenolic acid (MPA) is a potent **inhibitor** of mammalian **IMPDHs** but a poor **inhibitor** of microbial **IMPDHs**. MPA **inhibits** **IMPDH** by binding in the nicotinamide half of the dinucleotide site and trapping the covalent intermediate E-XMP. The MPA binding site of resistant **IMPDH** from the parasite Tritrichomonas foetuscontains two residues that differ from human **IMPDH**. Lys310 and Glu431 of T. foetus **IMPDH** are replaced by Arg and Gln, respectively, in the human type 2 enzyme. We characterized three **mutants** of T. foetusIMPDH: Lys310Arg, Glu431Gln, and Lys310Arg/Glu431Gln in order to determine if these substitutions account for the species selectivity of MPA. The **mutation** of Lys310Arg causes a 10-fold decrease in the K(i) for MPA **inhibition** and a 8-13-fold increase in the K(m) values for IMP and NAD(+). The **mutation** of Glu431Gln causes a 6-fold decrease in the K(i) for MPA. The double **mutant** displays a 20-fold increase in sensitivity to MPA. Pre-steady-state kinetics were performed to obtain rates of hydride transfer, NADH release, and hydrolysis of E-XMP for the **mutant IMPDHs**. The Lys310Arg **mutation** results in a 3-fold increase in the accumulation level of E-XMP, while the Glu431Gln **mutation** has only a minimal effect on the kinetic mechanism. These experiments show that 20 of the 450-fold difference in sensitivity between the T. foetus and human **IMPDHs** derive from the residues in the MPA binding site. Of this, 3-fold can be attributed to a change in kinetic mechanism. In addition, we measured MPA binding to enzyme adducts with 6-Cl-IMP and EICARMP. Neither of these adducts proved to be a good model for E-XMP.

L14 ANSWER 19 OF 45 CAPLUS COPYRIGHT 2003 ACS
AN 2000:628000 CAPLUS
DN 133:217680
TI Synergistic combinations of guanosine analog reverse transcriptase **inhibitors** and **inosine monophosphate dehydrogenase inhibitors** and their antiviral use
IN Margolis, David; Heredia, Alonso; Oldach, David
PA University of Maryland Biotechnology Institute, USA
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000051615	A1	20000908	WO 2000-US5731	20000303
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6514979	B1	20030204	US 1999-261712	19990303
PRAI US 1999-261712	A	19990303		

OS MARPAT 133:217680
AB The invention discloses synergistic combinations of guanosine nucleoside analog reverse transcriptase **inhibitors** (e.g. abacavir) with **inosine monophosphate dehydrogenase inhibitors** (e.g. mycophenolates), pharmaceutical compns. comprising such combinations, and therapeutic methods comprising administering the synergistic combinations to subjects in need thereof, for treating a viral (e.g. HIV-1) infection.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 4 MEDLINE
AN 1999322387 MEDLINE
DN 99322387 PubMed ID: 10390605
TI Novel mycophenolic adenine bis(phosphonate)s as potential immunosuppressants.
AU Pankiewicz K W; Lesiak-Watanabe K; Watanabe K A; Malinowski K
CS Pharmasset, Inc., 1860 Montreal Road, Atlanta, GA 30084, USA.
SO CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 629-34.
Journal code: 9440157. ISSN: 0929-8673.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991012
AB Mycophenolic acid (MPA) is the most potent and specific inhibitor of inosine monophosphate dehydrogenase (**IMPDH**). This compound was reported to bind the NAD site of **IMPDH** and mimic the binding of nicotinamide moiety of nicotinamide adenine dicnucleotide. We linked MPA derivatives with the adenine moiety of NAD through a methylenebis(phosphonate) bridge to form novel mycophenolic adenine dinucleotides (MADs) which resemble well the intact natural cofactor. The MAD analogues differ by the length of the side chain (linker) between the aromatic ring of mycophenolic derivative and the beta-phosphorus atom of the adenosine bis(phosphonate) moiety. Regardless of the linker size, MADs were found to be potent inhibitors of **human IMPDH** type I and type II with Ki's = 0.25-0.52 microM, an order of magnitude less potent than MPA itself (Ki = 0.01-0.04 microM). The growth of K562 cells was inhibited by MPA (IC50 = 0.03 microM) and the MAD analogues (IC50 = 0.01-1.15 microM) with a similar potency. Accordingly, a suppression of alloantigen- induced **proliferation** of **human** lymphoctyes by the MAD analogues at concentration of 10-20 microM was equally effective as that observed for MPA. In contrast to MPA, MAD analogues were found to be **resistant** to glucuronidation in vitro. Since therapeutic potential of MPA is limited by its undesirable glucuronidation, the glucuronidation- **resistant** MAD analogues may be superior immunosuppressants if they are not glucuronidated in vivo.

4 ANSWER 30 OF 45 MEDLINE DUPLICATE 10
AN 1999322381 MEDLINE
DN 99322381 PubMed ID: 10390599
TI Differential signatures of bacterial and mammalian IMP dehydrogenase enzymes.
AU Zhang R; Evans G; Rotella F; Westbrook E; Huberman E; Joachimiak A; Collart F R
CS Biosciences Division, Argonne National Laboratory.
SO CURRENT MEDICINAL CHEMISTRY, (1999 Jul) 6 (7) 537-43.
Journal code: 9440157. ISSN: 0929-8673.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 19991026
Last Updated on STN: 19991026
Entered Medline: 19991012
AB IMP dehydrogenase (**IMPDH**) is an essential enzyme of de novo guanine nucleotide synthesis. **IMPDH inhibitors** have clinical utility as antiviral, anticancer or immunosuppressive agents. The essential nature of this enzyme suggests its therapeutic applications may be extended to the development of antimicrobial agents. Bacterial **IMPDH** enzymes show biochemical and kinetic characteristics that are different than the mammalian **IMPDH** enzymes, suggesting **IMPDH** may be an attractive target for the development of antimicrobial agents. We suggest that the biochemical and kinetic differences between bacterial and mammalian enzymes are a consequence of the variance of specific, identifiable amino acid residues. Identification of these residues or combination of residues that impart this mammalian or bacterial enzyme signature is a prerequisite for the rational identification of agents that specifically target the bacterial enzyme. We used sequence alignments of **IMPDH** proteins to identify sequence signatures associated with bacterial or eukaryotic **IMPDH** enzymes. These selections were further refined to discern those likely to have a role in catalysis using information derived from the bacterial and mammalian **IMPDH** crystal structures and site-specific **mutagenesis**. Candidate bacterial sequence signatures identified by this process include regions involved in subunit interactions, the active site flap and the NAD binding region. Analysis of sequence alignments in these regions indicates a pattern of catalytic residues conserved in all enzymes and a secondary pattern of amino acid conservation associated with the major phylogenetic groups. Elucidation of the basis for this mammalian/bacterial **IMPDH** signature will provide insight into the catalytic mechanism of this enzyme and the foundation for the development of highly specific **inhibitors**.

RS 403.C8

L13 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 1997:57071 CAPLUS
DN 126:84296
TI Update on preclinical and clinical experience with mycophenolate mofetil
AU Sollinger, H. W.
CS Dep. Surg., Univ. Wisconsin Sch. Med., Madison, WI, 53792, USA
SO Transplantation Proceedings (1996), 28(6, Suppl. 1), 24-29
CODEN: TRPPA8; ISSN: 0041-1345
PB Appleton & Lange
DT Journal
LA English
AB A no. of excellent reviews have described in detail the discovery and rationale for the development of mycophenolate mofetil (MMF) as an immunosuppressive drug candidate. The goal of the original research initiated by Syntax was to identify new immunosuppressants for transplantation by finding ways to selectively interfere with the activation and **proliferation** of T- and B-lymphocytes. A genetic defect in the purine metab. of children with inherited adenosine deaminase deficiency was obsd. to correlate with reduced levels of T- and B-lymphocytes, although brain function and levels of other blood cells remained reasonably normal. This finding led to speculation that the **inhibition** of de novo purine synthesis in lymphocytes, by blocking the action of the enzyme **inosine monophosphate dehydrogenase** (**IMPDH**), could selectively **inhibit** the **proliferation** of T- and B-lymphocytes in preference to other cell types capable of using a salvage pathway for purine synthesis. Mycophenolic acid (MPA) (Fig 1), a fermn. product of several Penicillium species and a potent **inhibitor** of **IMPDH**, was selected for study in preference to nucleoside analogs, which risked **mutagenic** or other undesirable side effects. Addnl., MPA had been studied for some time as a possible treatment for tumors and psoriasis without reports of serious side effects. MMF is the morpholinoethyl ester of MPA (Fig 1), a deriv. specifically developed to improve the oral bioavailability of the drug; MMF is readily hydrolyzed in blood-cell culture or in vivo to give MPA. As outlined in the following section, preliminary in vitro and animal model studies quickly demonstrated that MMF was a potentially valuable immunosuppressive drug without serious side effects or limiting toxicity. These studies also established that the immunosuppressive effects of MMF are derived from a no. of consequences resulting from **IMPDH inhibition**: selective redn. of T- and B-lymphocyte **proliferation**, **inhibition** of antibody formation and, perhaps, even modification of cytokine prodn. in the immune response.

L13 ANSWER 5 OF 6 MEDLINE
AN 96252067 MEDLINE
DN 96252067 PubMed ID: 8680053
TI Purine metabolism and immunosuppressive effects of mycophenolate mofetil (MMF).
AU Allison A C; Eugui E M
CS Dawa Incorporated, Belmont, CA 94002, USA.
SO CLINICAL TRANSPLANTATION, (1996 Feb) 10 (1 Pt 2) 77-84. Ref: 33
Journal code: 8710240. ISSN: 0902-0063.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199608
ED Entered STN: 19960828
Last Updated on STN: 19960828
Entered Medline: 19960822
AB Mycophenolate mofetil (MMF) is a novel immunosuppressive drug that shows promise in preventing the rejection of organ allografts and in the treatment of ongoing rejection. Orally administered MMF is hydrolyzed by esterases in the intestine and blood to release mycophenolic acid (MPA), a potent, selective, noncompetitive **inhibitor** of the type 2 isoform of inosine monophosphate dehydroxygenase (**IMPDH**) expressed in activated human T and B lymphocytes. By **inhibiting** **IMPDH**, MPA depletes the pool of dGTP required for DNA synthesis. MPA has a more potent cytostatic effect on lymphocytes than on other cell types, and this is the principal mechanism by which immunosuppressive activity is exerted. MPA also depletes pools of GTP in human lymphocytes and monocytes, thereby **inhibiting** the synthesis of fucose- and mannose-containing saccharide components of membrane glycoproteins. These are recognized by the family of adhesion molecules termed selectins. By this mechanism, MPA could decrease the recruitment of lymphocytes and monocytes into sites of graft rejection. In addition to preventing allograft rejection, MMF suppresses graft-versus-host reactions in lethal and nonlethal murine models. MMF **inhibits** primary antibody responses more efficiently than secondary responses. MPA **inhibits** the **proliferation** of human B lymphocytes transformed by Epstein-Barr virus and is not **mutagenic**. Clinically attainable concentrations of MPA suppress the **proliferation** of human arterial smooth muscle cells. These two properties of MPA may decrease the risk of lymphoma development and proliferative arteriopathy in long-term recipients of MMF.